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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/677,592	MURRAY, ANDREW W.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 2, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on September 2, 2004 in response to the Restriction Requirement of June 2, 2004 is acknowledged and has been entered. Applicant has elected Group I, Claims 1-7, drawn to a method of identifying a drug that inhibits the growth or replication of a cell having a mutated MAD2 gene. Applicants further elect Tub1 as the single secondary gene.

Applicant's election with traverse of Group I, claims 1-7, drawn to a method of identifying a drug that inhibits the growth or replication of a cell having a mutated MAD2 gene has been acknowledged. The traversal is on the ground(s) that the inventive concept which links all of the pending claims is the realization that cells harboring a MAD2 mutation are useful targets for drug screening, particularly cancer drugs. Applicants further argue the invention would not require separate searching and examination because the various groups are linked through a single inventive concept, and do not represent distinct inventions that would. These arguments have been considered but are not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the restriction requirement of June 2, 2004.

As to the question of burden of search, the inventions are classified differently, necessitating different searches of the US Patents and literature. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-22 are currently pending in the application.

Claims 8-22 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-7 are currently under consideration.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the pending application, Serial Number 09/677,592 was not filed within twelve months from the filing of the provisional application, Serial Number 60/156,897. Therefore, the Examiner has determined the effective filing date to be **10/03/2000**.

Specification

The disclosure is objected to because it contains multiple embedded hyperlinks and/or other forms of browser-executable codes. See Page 1, Line 15; Page 5, Line 9; Page 20, Lines 8, 19-20; Page 21, line 7

Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable codes. See MPEP § 608.01.

Claim Objections

Claim7 is objected to because it recites multiple non-elected inventions such as: CIN8, SFI1, STU1 and combinations thereof. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are rejected as being vague and indefinite for reciting the term MAD2 in association with the growth and replication of cells as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify MAD2, for example, by SEQ ID NO: and function of MAD2.

Claim 7 is rejected as being vague and indefinite for reciting the term TUB1 in association with being a secondary gene as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify TUB1, for example, by SEQ ID NO: and function of TUB1.

Claims 1-2 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a control step, i.e. how the results compare to a cell grown without the drug.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of analogs and homologs of a genus of molecules referred to as "mutated MAD2". However, the written description appears to only sets forth a mutation in one species of MAD2 (Yeast) in association with a lethal screening strategy for identifying secondary targets.

The specification teaches (page 10, lines 10-11) that specific mutated MAD2 genes of the invention include, but are not limited to, molecules that contain a primary gene defect found in or associated with a tumor cell or cell affected with cell cycle regulation, which results in alteration, loss, or inhibition of a function, for example cellular function (page 11, lines 6-8). The specification further teaches (page 10, lines 12+) that the primary gene defect includes not only MAD2, but also any primary gene defect, wherein the defect is analogous or homologous to a defect found in or associated with a mammalian or human tumor cell or chromosomally aberrant cell. With regards to homologous, the specification teaches (page 10, lines 13-16) that homologous means a direct relationship among a "family" of genes in which certain sequences or domains are strongly conserved. For instance, MAD2 has 41% identity to Xenopus homolog and 40% identity to human homolog hsMAD2. With regards to analogous, the specification teaches (page 10, lines 16-20) "analogous" genes may serve similar or "analogous" functions, but are not directly related, i.e., sequences are not conserved. The specification (page 10-11, lines 25-5) also provides that specific MAD2 analogs and homologs of the invention include but are not limited to human mitotic feedback control protein, T-cell receptor alpha, human plasma membrane calcium pump, ... huntingtin, and RNA polymerase II (DNA directed) 220 kD protein. However, the written description (page 27, lines, 6+, Table 1) appears to only sets forth a mutation in one species of MAD2 (Yeast) in association with a lethal screening strategy for identifying secondary targets.
A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of molecules that encompass the genus of mutated MAD2 genes nor does it provide a description of structural features that are common to the molecules. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of a mutated MAD2 gene is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of mutated MAD2 genes, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only a mutated Yeast MAD2 gene, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-4, and 6-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Drubin *et al.* (U.S. Patent No. 5,972640, 1998).

(For the purposes of comparing the claims to the prior art, it is assumed for examination that MAD2 analogs or homologs encompass MAD)

In the instant case, the claims are drawn to a method of identifying a drug that inhibits the growth and replication of a cell having a mutated MAD2 gene or an analog or homolog thereof, comprising the steps of: (a) contacting a cell having a mutated MAD2 gene or an analog or homolog thereof with the drug; (b) determining whether the drug modulates the activity of a wildtype secondary gene present in combination with mutated MAD2 gene or an analog or homolog thereof, wherein the secondary gene is TUB1; (c) comparing the results of step (b) with a control cell grown without the drug, where in the control cell contains or does not contain mutated MAD2 gene.

Drubin *et al.* (column 1, lines 36-45) teaches a method of identifying an anti-mitotic agent comprising the steps of: (a) contacting a cell with an agent, wherein the cell has a functionally disrupted mitotic checkpoint; and (b) detecting the sensitivity or response of cells to the agent. The patent teaches (column 3 to 4, lines 66 to 4 respectively) that the method further comprises a negative control culture pair comprising first and second cells and an agent (e.g. solvent blank), wherein the first and second cells differ in that the second cell has a functionally disrupted mitotic checkpoint. With regards to the "functionally disrupted mitotic checkpoint", Drubin *et al.* teaches (column 3, lines 11-16) that the disruption may be affected by a variety of means including genetic disruption, e.g. genetic mutation in a spindle checkpoint component or target, such as a mad or bub gene. With regards to the cell, the patent teaches (claim column 4, lines 60-63) that plasmids bearing human α- and β-tubulin *(α-tubulin=TUB1)* genes are introduced into the yeast. The patent further teaches (column 4, lines 47-56) that antimitotic specificity of a compound is confirmed by

performing anti-tubulin immunofluoresence, which identifies spindle defects caused by the compound.

Although Drubin et al. does not specifically teach that α-tubulin (*TUB1*) is synthetically lethal when it is mutated, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure because the drug is modulating the activity of the wildtype TUB1 and not the mutated form. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drubin *et al.* (U.S. Patent No. 5,972640, 1998) in further view of Li *et al.* (Science 1996, 274, 5285; 246-248).

Drubin *et al.* teaches as set forth above with regard to claims 1, 3-4, and 6-7 a method of identifying an anti-mitotic agent comprising the steps of: (a) contacting a cell with an agent, wherein the cell has a genetic mutation in a spindle checkpoint component, such as a mad gene; and (b) detecting the sensitivity or response of cells to the agent. The patent also teaches (column 3 to 4, lines 66 to 4 respectively) that the method further comprises a negative control culture pair comprising first and second cells and an agent (e.g. solvent blank), wherein the first and second cells differ in that the second cell has a functionally disrupted mitotic checkpoint. Furthermore, Drubin et al. teach (column 2, lines 1-9) that this procedure utilizes cells characterized by a hypersensitivity to compounds that promote mitotic arrest, for example; unlike normal cells which arrest at the mitotic

phase when exposed to antimitotic agents, mitotic arrest mutants do not arrest the cell cycle in response to anti-mitotic compounds.

Drubin *et al.* does not teach that the cell or control cell is a tumor cell.

Li *et al* teaches (Title) the identification of human mitotic checkpoint gene: hsMAD2 which is 40% identical and 60% similar to the mitotic checkpoint gene MAD2 from the budding yeast Figure 1A). The reference also provides a nexus between the sensitivity of yeast and mammalian cells defective in mitotic checkpoint genes to mitotic spindle inhibitors. Specifically, the reference teaches (page 248, 2nd column, 1st paragraph) that human breast cell line T47D, which is sensitive to taxol and nocadazole, failed to undergo mitotic arrest and continued to divide 24 hours after nocodazole treatment, which suggests that these cell lines are defective in the mitotic checkpoint.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a tumor cell line defecting in a mitotic checkpoint gene for the purposes of identifying a drug that inhibits the growth and replication of cells. One would have been motivated to make these modifications because as evidenced by Li et al., it is well known in the art that mitotic checkpoint mutations are found in both yeast as well as tumor cell lines and that these cell lines are resistant to many commonly known anti-mitotic agents. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by combining a tumor cell line having a mutated MAD2 gene with the method for identifying anti-mitotic agents used by Drubin et al., one would achieve a method for identifying new anti-mitotic agents which are effective in cell lines having a mutated MAD2 gene.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
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BF

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PRIMARY EXAMINER